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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/977,702	11/13/92	PAPAYANNOPOULOU	T 92-678
18N2/0405			TENG, S EXAMINER
ALLEGRETTI AND WITCOFF, LTD. TEN SOUTH WACKER DRIVE CHICAGO, IL 60606			ART UNIT PAPER NUMBER 10
			1812
			DATE MAILED: 04/05/94

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

This application has been examined  Responsive to communication filed on 11/3/94  This action is made final

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.  
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- Notice of References Cited by Examiner, PTO-892.
- Notice of Draftsman's Patent Drawing Review, PTO-848.
- Notice of Art Cited by Applicant, PTO-1449.
- Notice of Informal Patent Application, PTO-152.
- Information on How to Effect Drawing Changes, PTO-1474.
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Part II SUMMARY OF ACTION

1.  Claims 12, 4, 5, 7, 8, 10, 11, 13, and 14 are pending in the application.  
Of the above, claims \_\_\_\_\_ are withdrawn from consideration.
2.  Claims 3, 6, 9, and 12 have been cancelled.
3.  Claims \_\_\_\_\_ are allowed.
4.  Claims 12, 4, 5, 7, 8, 10, 11, 13, and 14 are rejected.
5.  Claims \_\_\_\_\_ are objected to.
6.  Claims \_\_\_\_\_ are subject to restriction or election requirement.
7.  This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8.  Formal drawings are required in response to this Office action.
9.  The corrected or substitute drawings have been received on \_\_\_\_\_. Under 37 C.F.R. 1.84 these drawings are  acceptable;  not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-848).
10.  The proposed additional or substitute sheet(s) of drawings, filed on \_\_\_\_\_, has (have) been  approved by the examiner;  disapproved by the examiner (see explanation).
11.  The proposed drawing correction, filed \_\_\_\_\_, has been  approved;  disapproved (see explanation).
12.  Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has  been received  not been received  been filed in parent application, serial no. \_\_\_\_\_; filed on \_\_\_\_\_.
13.  Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14.  Other

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1. Claims 1, 2, 4, 5, 7, 8, 10, 11, 13, and 14 are pending in the instant application.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 1, 2, 4, 5, 7, 8, 10, 11, 13, and 14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, it is not clear as to what steps for blocking the VLA-4 antigen are encompassed by the claim. Do the steps include isolating the fibronectin or VCAM-1, generating VLA-4 antibodies, and administration of the blocking agent to a patient diagnosed with leukemia? The claim should set forth the method steps in a positive sequential manner.

4. Claims 1, 2, 4, 5, 7, 8, 10, 11, 13, and 14 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the anti-VLA-4 antibody alone or with a cytokine. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The rejection is maintained for reasons set forth in the previous Office action and stated below.

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Applicant arguments have been considered but are not deemed to be persuasive because the antibodies used in the examples and the claimed VCAM-1 and fibronectin molecules are very different proteins. Applicant has not provided in vivo data showing fibronectin, fibronectin peptides, soluble VCAM-1, or VCAM-1 peptides can peripheralize CD34<sup>+</sup> cells. Each of the claimed polypeptides and peptides bind to VLA-4 with a different affinity. Thus, it is unpredictable whether the binding affinity of the VCAM-1 or fibronectin molecules is sufficient to block VLA-4 antigen and to mobilize the CD34<sup>+</sup> cells.

5. Claims 1, 2, 4, 5, 7, 8, 10, 11, 13, and 14 are rejected under 35 U.S.C. § 103 as being unpatentable over Haas et al. or Craig et al. in view of Teixido et al. (1991) or Williams et al.

The rejection is maintained for reasons set forth in the previous Office action and stated below.

Applicant argue that there is no suggestion in the cited references to combine the teachings. This is deemed not to be persuasive because the motivation for combining the teachings could be based on scientific reasonings and does not have to be disclosed in the cited references. Peripheralization of stem cells with different agents is well known in the art. For example, the primary references teach the use of GM-CSF, SCF, or IL-3 to increase the number of stem cells in the peripheral

blood. It is also known that in normal hematopoiesis, the hematopoietic stem cells are confined to the bone marrow to mature. In addition, Teixido et al. (abstract) and Williams et al. (page 440) teach that progenitor cells, such as CD34<sup>+</sup> and CFU-S<sub>12</sub>, adhere to the bone marrow stromal cells via the VLA-4 antigen expressed on progenitor cells and the VCAM or fibronectin protein expressed by the stromal cells. Therefore, the skilled artisan would have reasonably expected that blocking the adhesion of VLA-4 antigen to the stromal cells would free the stem cells from the bone marrow stroma and would increase mobilization of the stem cells into the peripheral blood. Since Teixido et al. and Williams et al. show that anti-VLA-4 antibodies, VCAM molecule, and fibronectin peptide are capable of blocking the adhesion of progenitor cells to bone marrow stroma, it would have been obvious to the skilled artisan at the time the invention was made to modify the methods of peripheralizing stem cells disclosed by the primary references by adding a VLA-4 blocking agent, such as the anti-VLA-4 antibodies, the VCAM peptides, or the fibronectin peptides. Although the secondary references do not discuss methods for increasing the number of stem cells in the peripheral blood, the skilled artisan would have concluded from the teachings of the secondary references that the addition of a VLA-4 blocking agent would increase peripheralization of the CD34<sup>+</sup> cells. Consequently, one having ordinary skill in the art

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would have been motivated to combine the primary and the secondary references for increasing peripheralization of CD34<sup>+</sup> cells.

Thus, the claims are prima facie obvious over the prior art.

6. No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication should be directed to Sally Teng, Ph.D., at telephone number (703) 308-4230.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4227.

Sally Teng  
March 24, 1994

*Robert J. Hill Jr.*  
ROBERT J. HILL, JR.  
SUPERVISORY PATENT EXAMINER  
GROUP 1800